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Effective and selective iodofunctionalisation of organic molecules in water using the iodine–hydrogen peroxide tandem†

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Efficient hydrogen peroxide enhanced iodofunctionalisation of ketones, 1,3-dicarbonyl derivatives and activated aromatic molecules using elemental iodine in water is achieved, whereas alkynes were stereoselectively converted into (*E*)-1,2-diiodoalkenes.

Iodinated organic molecules are useful intermediates and synthons in organic synthesis, particularly in numerous carbon–carbon bond forming and iodine–metal exchange reactions.[1] In addition, a significant number of iodo-substituted molecules possess biological activity and their properties have attracted considerable attention in various fields of human and animal medicine.[2]

Several approaches to the introduction of an iodine atom into organic molecules are known. The most conventional strategies involve I+ reagents, iodides and iodine in combination with an oxidiser as the iodine atom sources.[3] Of these possibilities, elemental iodine is the reagent of choice, and its mild and clean activation is of wide interest.[4] Ever increasing 'green' requirements have resulted in wider use of cleaner solvents; water is one of the most important ones,[5] and several halogenation reactions in water/cosolvent are known,[6] though few in water alone have been reported.[7]

Here we report the efficient iodofunctionalisation of various types of organic molecules using elemental iodine, enhanced by 30% aqueous hydrogen peroxide in water without an organic cosolvent or other additives. A diluted aqueous solution of hydrogen peroxide is a highly convenient, safe and environmentally favourable oxidiser, and its utility is well exploited.[8] Initially, we reacted ketones **1** with 0.5 equiv. of I_2 in water and α-iodoketones **2** were obtained in 50% yield; on the other hand, addition of 1 equiv. of 30% aqueous H_2O_2 crucially enhanced iodine consumption, and the results are presented in Table 1. In a typical experiment‡ a mixture of 1-indanone **1a**, iodine and 30% H_2O_2 solution in water was stirred at room temperature and after a work-up procedure 2-iodo-1-indanone **2a**, was isolated in good yield. 1-Tetralone **1b** was transformed into **2b**, 5-nonanone **1c** exhibited similar reactivity producing **2c**, while cyclododecanone **1d** was converted into **2d**. Uracil **1e** was selectively transformed into biologically important 5-iodouracil **2e** in high yield. Table 2 summarizes the results of the iodination of 1,3-dicarbonyl derivatives **3** with the above mentioned system. 1,3-Diphenylpropan-1,3-dione **3a** was treated with 0.5 equiv. of I_2 and 1 equiv. of a 30% aqueous solution of H_2O_2 in water and converted into its 2-iodo derivative **4a**. α-Unsubstituted β-keto ester **3b** was transformed into ethyl 2-iodo-3-oxo-3-phenylpropanoate **4b** with 0.5 equiv. of I_2 and only 0.5 equiv. of aqueous H_2O_2, while ethyl 2-oxocyclopentanecarboxylate **3c** was derivatized into its 2-iodo analogue **4c**.

Table 1 Aqueous H_2O_2 enhanced iodination of ketones **1** by elemental iodine in water[a]

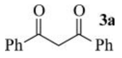
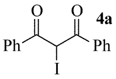
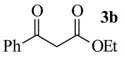
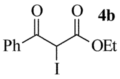
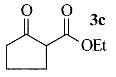
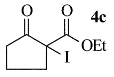
Entry	Substrate	Product	Yield (%)[b]
1	1-Indanone **1a**	2-Iodo-1-indanone **2a**	83
2	1-Tetralone **1b**	2-Iodo-1-tetralone **2b**	85
3	5-Nonanone **1c**	4-Iodo-5-nonanone **2c**	85
4	Cyclododecanone **1d**	2-Iodo-cyclododecanone **2d**	84
5	Uracil **1e**	5-Iodouracil **2e**	86[c]

[a] *Reagents and conditions*: substrate 1 mmol, I_2 0.5 mmol, H_2O_2 as 30% aqueous solution 1 mmol, H_2O 5 ml, (entries 1–4) T = 20 °C, rt = 18 h, (entry 5) T = 50 °C, rt = 7 h. [b] Isolated yield. [c] After crystallisation.

We also investigated the reactions of the $I_2/H_2O_2/H_2O$ reaction triad with aromatics **5**, bearing an activated ring; the results are presented in Table 3. Phenol **5a** was transformed into a mixture of 2-iodophenol **6a** and 2,6-diiodophenol **6a′** (rel. ratio 2/1), 4-iodophenol was not formed. Similarly, reaction of 4-*tert*-butylphenol **5b** led to a mixture of 2-iodo-4-*tert*-butylphenol **6b** and 2,6-diiodo-4-*tert*-butylphenol **6b′** (rel. ratio 6/1). 3′,5′-Dihydroxyacetophenone **5c** exhibited completely prevailing reactivity of the aromatic ring over the α-keto position, producing 3′,5′-dihydroxy-4′-iodoacetophenone **6c**. Amino functionality was also compatible with the new reaction system. Reaction of *N,N*-diethylaniline **5d** regioselectively led to the 4-iodo derivative **6d**, whereas aniline **5e** exclusively produced 4-iodoaniline **6e**, in contrast to phenol, no *ortho* substitution was observed. Derivatization of 1,3-dimethoxybenzene **5f** resulted in formation of 1,3-dimethoxy-4-iodobenzene **6f** in high yield, while 1,3,5-trimethoxybenzene **5g** selectively afforded 2-iodo-1,3,5-trimethoxybenzene **6g**.

There are some reports of stereoselective addition of I_2 to alkynes.[9] We found that water is a suitable reaction medium for the addition of I_2 to sp-hybridized atoms: alkynes **7** were stereoselectively transformed to (*E*)-1,2-diiodoalkene derivatives **8** in good yields (Table 4). Transformation of terminal **7a** with 1 equiv. of I_2

Table 2 Iodofunctionalisation of 1,3-dicarbonyl substrates **3** with the H_2O_2/I_2 system in water[a]

Entry	Substrate	*t*/h	*T*/°C	Product	Yield (%)
1	 **3a**	20	20	 **4a**	92[b]
2	 **3b**	5	20	 **4b**	69[c]
3	 **3c**	5	20	 **4c**	90[d]

[a] *Reagents and conditions*: substrate 1 mmol, I_2 0.5 mmol, H_2O_2 as 30% aq. sol. 1 mmol (in case of **3b** 0.5 mmol of H_2O_2 was used), H_2O 5 ml. [b] Isolated yield after crystallisation. [c] Isolated yield after flash chromatography. [d] Decomposition on SiO_2, 90% conversion of **3c** detected from ^1H NMR.

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† Electronic supplementary information (ESI) available: validation details and spectroscopic data for compounds **4c** and **6c**. See http://www.rsc.org/suppdata/cc/b4/b409919b/

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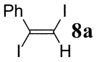
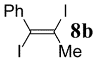
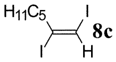
Table 3 Iodine transfer to activated aromatic molecules **5** enhanced by 30% aqueous H_2O_2 in water[a]

Entry	Substrate	T/°C	t/h	Product	Yield (%)[b]
1	Phenol **5a**	20	18	2-Iodophenol **6a** 2,6-Diiodophenol **6a′**	50 25
2	4-*tert*-Butylphenol **5b**	55	4.5	4-*tert*-Butyl-2-iodophenol **6b** 4-*tert*-Butyl-2,6-diiodophenol **6b′**	73 12
3	3′,5′-Dihydroxyacetophenone **5c**	45	3.5	3′,5′-Dihydroxy-4′-iodoacetophenone **6c**	85[c]
4	*N*,*N*-Diethylaniline **5d**	20	18	4-Iodo-*N*,*N*-diethylaniline **6d**	83
5	Aniline **5e**	20	18	4-Iodoaniline **6e**	87
6	1,3-Dimethoxybenzene **5f**	50	5	4-Iodo-1,3-dimethoxybenzene **6f**	92[d]
7	1,3,5-Trimethoxybenzene **5g**	50	7	2-Iodo-1,3,5-trimethoxybenzene **6g**	90

[a] *Reagents and conditions*: (entries 1–3, 6, 7) substrate 1 mmol, I_2 0.5 mmol, H_2O_2 as 30% aq. solution 1 mmol (2 mmol in case of **5g**), H_2O 5 ml; (entries 4, 5) substrate 1.0 mmol, I_2 0.5 mmol, H_2O_2 as 30% aq. solution 0.8 mmol, H_2O 5 ml. [b] Isolated yield. [c] After crystallisation. [d] 3% of 2,4-diiodo-1,5-dimethoxybenzene was formed.

Table 4 Iodination of alkynes **7** with I_2 in water[a]

Entry	Alkyne	Product	Yield (%)[b]
1	PhC≡CH **7a**	 **8a**	83
2	PhC≡CMe **7b**	 **8b**	92
3	1-Heptyne **7c**	 **8c**	80

[a] *Reagents and conditions*: substrate 1 mmol, I_2 1 mmol, H_2O 5 ml, T = 20 °C, rt = 18 h. [b] Isolated yield.

in water resulted in the formation of (*E*)-1,2-diiodo-1-phenylethene **8a**. Similarly, reaction of 1-phenyl-1-propyne **7b** with I_2 afforded (*E*)-1,2-diiodo-1-phenylpropene **8b** in almost quantitative yield, while aliphatic 1-heptyne **7c** was derivatized into (*E*)-1,2-diiodo-1-heptene **8c**.

In conclusion, several comparative advantages of the new method for the introduction of an iodine atom into organic molecules should be stressed. Reactions were performed in water without an organic cosolvent, iodine is completely consumed, and the culminating point of the waste-minimising and simple reaction protocol is the utility of a 30% aqueous solution of H_2O_2.

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Notes and references

‡ A typical experimental procedure is as follows: to a suspension of substrate **1**, **3** or **5** (1 mmol) in H_2O (5 ml), 30% aqueous solution of H_2O_2 (1 mmol) and I_2 (0.5 mmol) were added and the reaction mixture stirred at room or elevated temperature until iodine consumption. An identical procedure was used in the case of alkynes **7**, except for H_2O_2. Oily products were extracted from the reaction mixture with CH_2Cl_2, solid products were obtained after suction–filtration, washed with a 5% aqueous solution of $Na_2S_2O_3$, water and dried. Crude reaction mixtures were analysed by TLC, ^1H NMR and MS. Products were isolated by flash chromatography over SiO_2 or by preparative TLC or crystallisation. The spectroscopic characteristics of already known products were compared with published data, while the new compounds were validated as stated in the ESI.†

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